

BEFORE THE  
THE TECHNICAL REPORTS REVIEW SUBCOMMITTEE  
OF THE NATIONAL TOXICOLOGY PROGRAM  
BOARD OF SCIENTIFIC COUNSELORS

COMMENTS OF THE  
ALKANOLAMINES PANEL OF THE  
AMERICAN CHEMISTRY COUNCIL  
ON NTP'S DRAFT TECHNICAL REPORT

---

National Toxicology Program (NTP) Board  
of Scientific Counselors Meeting; Review  
of Draft NTP Technical Report on the Toxicology  
and Carcinogenesis Studies of Triethanolamine in  
B6C3F<sub>1</sub> Mice (Dermal Study);  
68 Fed. Reg. 18666 (Apr. 16, 2003)

---

Courtney M. Price  
Vice President  
CHEMSTAR

Jonathon T. Busch  
Manager, Alkanolamines Panel

David F. Zoll, Esquire  
Vice President and  
General Counsel

Theodore R. Waugh, Esquire  
Counsel, CHEMSTAR

Of Counsel:

Lynn L. Bergeson, Esquire  
Lisa M. Campbell, Esquire  
Richard P. Bozof, Esquire  
Bergeson & Campbell, P.C.  
1203 Nineteenth Street, N.W.  
Suite 300  
Washington, D.C. 20036-2401

May 14, 2003

AMERICAN CHEMISTRY COUNCIL  
1300 Wilson Boulevard  
Arlington, VA 22209  
(703) 741-5000

## EXECUTIVE SUMMARY

The Alkanolamines Panel (Panel) of the American Chemistry Council submits these comments on the National Toxicology Program's (NTP) draft Technical Report (Draft Report) on the Toxicology and Carcinogenesis Studies of Triethanolamine in B6C3F<sub>1</sub> Mice (Dermal Study), scheduled for peer review on May 22, 2003. The Panel is composed of major producers of alkanolamines, including producers of triethanolamine (TEA).

The Panel has the following concerns with the Draft Report.

- The Draft Report should acknowledge and discuss certain confounding factors in the Dermal Study necessary for the scientifically appropriate interpretation of the results.
  - Because of the strong potential for oral exposure to TEA in the Dermal Study, the Draft Report should indicate that the Dermal Study should be considered a combined oral and dermal exposure study.
  - The Draft Report should acknowledge that the use of obese mice confounded the Dermal Study with respect to the interpretation of the observed increase of benign liver tumors in the female mice.
- The Discussion Section of the Draft Report inappropriately discusses or alludes to the results of discredited studies and should be revised.

## TABLE OF CONTENTS

EXECUTIVE SUMMARY .....	i
TABLE OF CONTENTS.....	ii
INTRODUCTION .....	1
I. THE DRAFT REPORT SHOULD ACKNOWLEDGE AND DISCUSS CERTAIN CONFOUNDING FACTORS IN THE DERMAL STUDY NECESSARY FOR THE SCIENTIFICALLY APPROPRIATE INTERPRETATION OF THE RESULTS .....	2
A. Because of the Strong Potential for Oral Exposure to TEA in the Dermal Study, the Draft Report Should Indicate That the Dermal Study Should Be Considered a Combined Oral and Dermal Exposure Study.....	3
B. The Draft Report Should Acknowledge That the Use of Obese Mice Confounded the Dermal Study with Respect to the Interpretation of the Observed Increase of Benign Liver Tumors in the Female Mice .....	3
II. THE DISCUSSION SECTION OF THE DRAFT REPORT ADDRESSING RESULTS OF DISCREDITED STUDIES SHOULD BE REVISED .....	4
CONCLUSION.....	5

## INTRODUCTION

The Alkanolamines Panel (Panel) of the American Chemistry Council submits these comments on the National Toxicology Program's (NTP) draft Technical Report (Draft Report) on the Toxicology and Carcinogenesis Studies of Triethanolamine in B6C3F<sub>1</sub> Mice (Dermal Study),<sup>1</sup> scheduled for peer review on May 22, 2003. The Panel is composed of major producers of alkanolamines, including producers of triethanolamine (TEA).<sup>2</sup>

The Draft Report reports an increase in benign neoplasms (hepatocellular adenomas) in all treatment groups compared to controls in the female mice. It also reports a marginal increase in hemangiosarcomas of the liver at the mid-dose in the male mice, but reported no increases in that tumor at any other dose.<sup>3</sup> The Draft Report concludes that under the conditions of the study there was "some evidence of carcinogenic activity" of TEA in female B6C3F<sub>1</sub> mice based on the reported increased incidences of hepatocellular adenoma and that there was "equivocal evidence of carcinogenic activity" of TEA in male B6C3F<sub>1</sub> mice based on the occurrence of liver hemangiomas.<sup>4</sup>

---

<sup>1</sup> NTP, *NTP Technical Report on the Toxicology and Carcinogenesis Studies of Triethanolamine (CAS No. 102-71-6) in B6C3F<sub>1</sub> Mice (Dermal Study)*, NTP TR 518, NIH Publication No. 03-4452.

<sup>2</sup> The Panel members are: BASF Group, The Dow Chemical Company, Equistar Chemical, L.P., Huntsman Corporation, and Ineos LLC.

<sup>3</sup> Draft Report at 6.

<sup>4</sup> *Id.* at 7.

As discussed in detail below, the Draft Report should acknowledge and discuss certain confounding factors in the Dermal Study necessary for the scientifically appropriate interpretation of the results. Moreover, certain technical corrections should be made to the Discussion Section of the Draft Report. Additionally, to the extent the Discussion Section addresses studies other than the Dermal Study, the several negative carcinogenicity bioassays on TEA, such as the Konishi, *et al.* (1992) study, summarized in the Introduction Section of the Draft Report, should also be noted.

I. THE DRAFT REPORT SHOULD ACKNOWLEDGE AND DISCUSS CERTAIN  
CONFOUNDING FACTORS IN THE DERMAL STUDY NECESSARY FOR THE  
SCIENTIFICALLY APPROPRIATE INTERPRETATION OF THE RESULTS

The Draft Report, to provide a more full evaluation of the Dermal Study results, should acknowledge and explain that the exposed animals likely had significant oral exposure in addition to dermal exposure and that any TEA-associated increases in the benign liver tumors in females likely were associated with a combination of both routes of exposure. The Draft Report should also acknowledge and explain that the obesity of the female mice was a potentially confounding factor in the Dermal Study in that it represents an additional risk factor of unknown consequence in the presence of an administered chemical.

A. Because of the Strong Potential for Oral Exposure to TEA in the Dermal Study, the Draft Report Should Indicate That the Dermal Study Should Be Considered a Combined Oral and Dermal Exposure Study

A portion of the dosing in the Dermal Study likely occurred by the oral, rather than the dermal, route. TEA was “painted” on the backs of the mice, and the skin was not covered to prevent the ingestion of TEA. Mice can easily reach their dorsal surfaces with their fore or hind limbs during grooming. Thus, as a result of grooming, the animals likely ingested a significant amount of TEA, resulting in higher blood levels of TEA than would be obtained if strictly dermal administration had been maintained.<sup>5</sup> This introduces uncertainty in both the route of exposure and the dose and confounds the results of the study as solely a dermal study. Moreover, ingestion is not a relevant route of human exposure, since TEA is not used in products intended to be ingested. These considerations should be acknowledged and discussed in the Draft Report.

B. The Draft Report Should Acknowledge That the Use of Obese Mice Confounded the Dermal Study with Respect to the Interpretation of the Observed Increase of Benign Liver Tumors in the Female Mice

Female mice in the Dermal Study became very obese by maturity.<sup>6</sup> Obesity is a known risk factor for cancer in mice. Recent studies have demonstrated a strong correlation

---

<sup>5</sup> This conclusion is supported by a study on diethanolamine (DEA) in which mice dosed with DEA via skin painting with oral access to the application site were found to have approximately 35% higher blood levels of DEA than identically dosed mice having no oral access to the application site. (Stott *et al.*, (2000) *Toxicology Letters*. 114; 67-75).

<sup>6</sup> Body weights of female mice were approximately 20% higher than in female mice in the original NTP mouse bioassay. Draft Report at 58.

between body weight and the development of liver tumors in B6C3F<sub>1</sub> mice.<sup>7</sup> Even where the background rate of hepatocellular tumors in the controls is not extraordinarily high, obesity itself is a risk factor that may enhance a tumorigenic response to a chemical in the liver of B6C3F<sub>1</sub> mice. This consideration should be acknowledged and discussed in the Draft Report.

## II. THE DISCUSSION SECTION OF THE DRAFT REPORT ADDRESSING RESULTS OF DISCREDITED STUDIES SHOULD BE REVISED

The Discussion Section includes inaccurate or misleading statements about discredited positive studies on TEA. For example, it states that the “results reported here are consistent with those reported in [the original NTP mouse study on TEA].”<sup>8</sup> Given that the original study was ultimately determined, after peer review, to be an “inadequate study” as a result of the confounding effects of the *Helicobacter hepaticus* infection, any comparison of the tumorigenic results of the Dermal Study to the original study is inappropriate. In any event, the tumorigenic results in the Dermal Study are not consistent with the results in male mice in the original study.<sup>9</sup>

---

<sup>7</sup> International Life Sciences Institute (ILSI), Fifth Workshop on Mouse Liver Tumors, Summary Report (Nov. 7-9, 1994) at 3, 45, 60-61 (ILSI Report).

<sup>8</sup> Draft Report at 58.

<sup>9</sup> We also note that the Draft Report states that NTP had *proposed* that the original NTP study in male mice be considered inadequate based on the *H. hepaticus* infection in that study. *Id.* at 57. In fact, NTP reached this conclusion only in the final report on the original study after peer review.

As a further example, the Discussion Section also refers to the highly discredited and flawed Hoshino and Tanooka (1978) study.<sup>10</sup> The Discussion Section should not include any discussion of this study. To the extent the Discussion Section discusses the results of any carcinogenicity studies on TEA other than the Dermal Study, it should note the several negative carcinogenicity studies on TEA, which are mentioned in the Introduction Section of the Draft Report, such as the Konishi, *et al.* (1992) study.<sup>11</sup>

### CONCLUSION

For the reasons stated above, the Draft Report should acknowledge and discuss the confounding factors of multiple routes of exposure (oral and dermal) and obesity in the Dermal Study that are necessary for the scientifically appropriate interpretation of the results. Further, certain technical corrections should be made in the Discussion Section of the Draft Report. Additionally, to the extent the results of carcinogenicity studies other than the Dermal Study are discussed or alluded to in the Discussion Section, the results of the several negative cancer studies on TEA should be included.

---

<sup>10</sup> The flaws of this study are described in Knaak, J.B., Leung, H., Stott, W.T., Busch, J., and Bilsky, J. (1997). "Toxicology of Mono-, Di-, and Triethanolamine," at 57-58, Volume 149, *Reviews of Environmental Contamination and Toxicology*, and by IARC, *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans -- Volume 77: Some Industrial Chemicals* (2000), at 386.

<sup>11</sup> See Draft Report at 25-27. Although IARC issued its monograph on TEA before issuance of the Draft Report, the Draft Report should also note in the Introduction and the Discussion, if other studies are discussed, that IARC determined that there was inadequate evidence both in experimental animals and in humans for the carcinogenicity of TEA. IARC Monograph at 398.